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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

WEHBE, ANNE MARIE SABRINA

ART UNIT	PAPER NUMBER
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1632

DATE MAILED: 11/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/744,654

Applicant(s)

LAPIDOT ET AL.

Examiner

Anne Marie S. Wehbe

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 13 September 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 123-126 and 128-131 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 123-126, and 128-131 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date. _____ | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

Applicant's amendment and response received on 9/13/04 has been entered. Claims 1-122, and 127 are canceled. New claims 129-131 have been entered. Claims 123-126, and 128-131 are currently pending and under examination. An action on the merits follows.

Those sections of Title 35, not included in this office action can be found in the previous office action.

Claim Rejections - 35 USC 103

The rejection of previously pending claims 15-21, 23-27, 33, 48-49, 117-122, and 127-128 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 5,541,103, 7/30/96, hereafter referred to as Kanz et al. in view of Mohle et al. (1998), Blood, Vol. 91, No. 12, 4523-4530, is withdrawn over canceled claims 15-21, 23-27, 33, 48-49, 117-122, and 127, maintained over amended claim 128, and newly applied to amended claims 123-126, and 129-131. Since claims 123-126 and 129-131 were not previously included in this rejection, and since their inclusion in this rejection is not the result of the amendments to these claims, this office action has been made **non-final**.

Applicant's amendments to the claims and arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection over claims 123-126 and 128-131.

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The applicant argues that claims 123-126 were not included in this rejection in the previous office action and that they have been amended to include the limitations of the rejected base and intervening claims. The office acknowledges that claims 123-126 were not included in the rejection under 103 over Kanz et al. in view of Mohle in the previous office action. However, upon further consideration, the examiner finds that these claims should in fact have been included in the rejection. As such, amended and new claims 123-126 and 128-131 have been rejected in the instant office action as being non-obvious in view of the combined teachings of Kanz et al. in view of Mohle. Since the exclusion of these claims from the rejection of record was an error on the part of the office, this office action is non-final.

The rejection of record as it applies to the instant claims is reiterated below for clarity of prosecution. Kanz et al. teaches the preparation of hematopoietic stem cells useful for transplantation comprising stimulating cells with mixtures of cytokines including SCF-1 and IL-6 (Kanz et al., columns 1 and 7-8). In particular, Kanz et al. teaches that CD34+ cells treated with SCF-1 and IL-6 expand in culture and demonstrate increased colony forming potential which increases their usefulness for transplantation (Kanz et al., columns 3-4). It is further noted that Kanz et al. teaches the stimulation of the cells with the growth factor for “up to 28 days” (Kanz et al, column 6, line 25). Kanz et al. also teaches the stimulation of peripheral blood progenitor cells derived from cancer patients , and further suggests purifying the expanded peripheral blood progenitor cells from contaminating tumor cells (Kanz et al., column 4, lines 19-31). Please note that while Kanz et al. does not specifically teach that the administration of SCF-1 and IL-6 results in increased expression of CXCR4 on the progenitor cells, Kanz et al. does teach the exact method steps recited by the claims for up-regulating surface CXCR4

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expression. The MPEP states that, "Where the claimed and prior art products are identical or substantially identical in structure or compositions, or are produced by identical or substantially identical processes, a *prima facie* case of either anticipation or obviousness has been established. MPEP 211.01 and *In re Best*, 195 USPQ 430, 433 (CCPA 1997).

Kanz et al. does not specifically teach the sorting of expanded cells that migrate in response to SDF-1 or which adhere to stromal cells. Mohle et al. supplements Kanz et al. by teaching the sorting of CXCR4⁺ cells from a population of primitive hematopoietic progenitor cells characterized as CD34⁺/CD38^{-low} by carrying out an *in vitro* transmigration assay across a mechanical barrier of cells wherein the cells to be sorted are the CXCR4⁺ cells which transmigrate in response to culture supernatant containing SDF-1 (Mohle et al., page 4524, column 2, and pages 4526-4527 and Figure 2). Mohle et al. further teaches that the culture supernatant containing SDF-1 is derived from MS-5 bone marrow stromal cells. Mohle et al. further teaches that CXCR4⁺ hematopoietic progenitor cells which migrate in response to SDF-1 would have enhanced capability to migrate and home to the bone marrow which would increase their usefulness for transplantation (Mohle et al., pages 4523 and 4528).

Based on the motivation provided by Mohle et al. for sorting primitive CXCR4⁺ CD34⁺ CD38^{-low} hematopoietic progenitor cells which transmigrate in response to SDF-1 for use in transplantation in order to increase stem cell homing and migration, it would have been *prima facie* obvious to further purify the stem cells produced by Kanz et al. by using the transmigration assay taught by Mohle et al. In view of the successful use of the transmigration assay to isolate CXCR4⁺ stem cells which migrate in response to SDF-1 by Mohle et al., the skilled artisan would have had a reasonable expectation of success in using this methods to sort stem cells

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produced by the methods of Kanz et al. that migrate in response to SDF-1 and which are CXCR4+ and CD38^{-low}.

In regards to the limitation in the claims that the stem cells are stimulated for “up to five days”, Kanz et al. teaches a range of “up to 28 days”. Thus, the range recited in the claims lies within the range taught by Kanz et al. The applicant is reminded that the MPEP states that, “ In the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a prima facie case of obviousness exists. *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990)” MPEP 2144.05.

The applicant also argue that they have shown “unexpected results”, citing the examples and the post-filing reference by Kollett et al. However, the previous office action stated that the applicants have not met the requirements for establishing “unexpected results” regarding the methods as claimed as set forth in MPEP 716.02. Regarding allegations of “unexpected results”, the MPEP states that the arguments of counsel cannot take the place of evidence in the record . *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716,718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results. MPEP 716.01(c). Therefore, applicant’s arguments regarding “unexpected results” are not compelling in the absence of evidence in the form of a declaration or affidavit. Regarding Kollett et al, it appears that the applicant has included this reference to demonstrate that cytokines other than SCF can be used to upregulate CXCR4 expression. The office acknowledges that Kollett et al. teaches that HGF can be used to increase CXCR4 surface expression in primitive CD34+ cells. However, neither the

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statements of the applicant's representative, nor the post-filing teachings of Kollett et al. provide the requisite evidence for "unexpected results" required to overcome the rejection of record.

Claim Rejections - 35 USC 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 123-124 and 128-129 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims have been amended to recite methods for the preparation of a cell composition consisting essentially of human hematopoietic CD38^{-/low} CXCR4⁺ stem cells. However, the claims further recite wherein said composition consisting essentially of CD38^{-/low} CXCR4⁺ stem cells are selected from a group which includes CXCR4^{-/low} stem cells that , "have the potential to express CXCR4 on the cell surface". It is unclear how cells which are CXCR4^{-/low} meet the initial claim limitation of cells which are CXCR4⁺. While the claim indicates that the CXCR4^{-/low} cells can be stimulated to express CXCR4, a cell which has the "potential" to express CXCR4 is not the same as a cell which actually expresses CXCR4 and is considered CXCR4⁺. As such, the claims are confusing in that it is unclear which cell population the applicant wishes to claim, CD38^{-/low} CXCR4⁺ cells or CD38^{-/low} CXCR4^{-/low} cells. Further, the method steps recited appear to generate CD38^{-/low} CXCR4⁺ cells not CD38^{-/low} CXCR4^{-/low} cells. Therefore, the metes and bounds of the claims cannot be determined.

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No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. The examiner can be reached Monday- Friday from 10:30-7:00 EST. If the examiner is not available, the examiner's supervisor, Amy Nelson, can be reached at (571) 272-0804. For all official communications, the technology center fax number is (703) 872-9306. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER

A handwritten signature in black ink, appearing to read 'Anne M. Wehbé', with a stylized flourish at the end.